COLLEGE OF ENGINEERING
INDUSTRIAL & OPERATIONS ENGINEERING
UNIVERSITY OF MICHIGAN

Mathematical Programming Models for Optimization of Medical Decision Making

Vietnam – USA Join Mathematical Meeting

Quy-Nhon – Vietnam, June 2019

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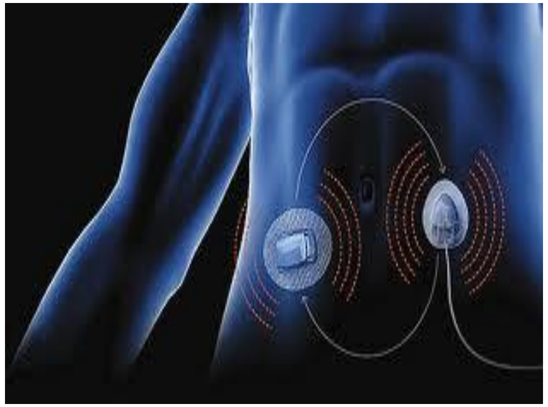
Optimization in Medicine

Cancer

Diabetes



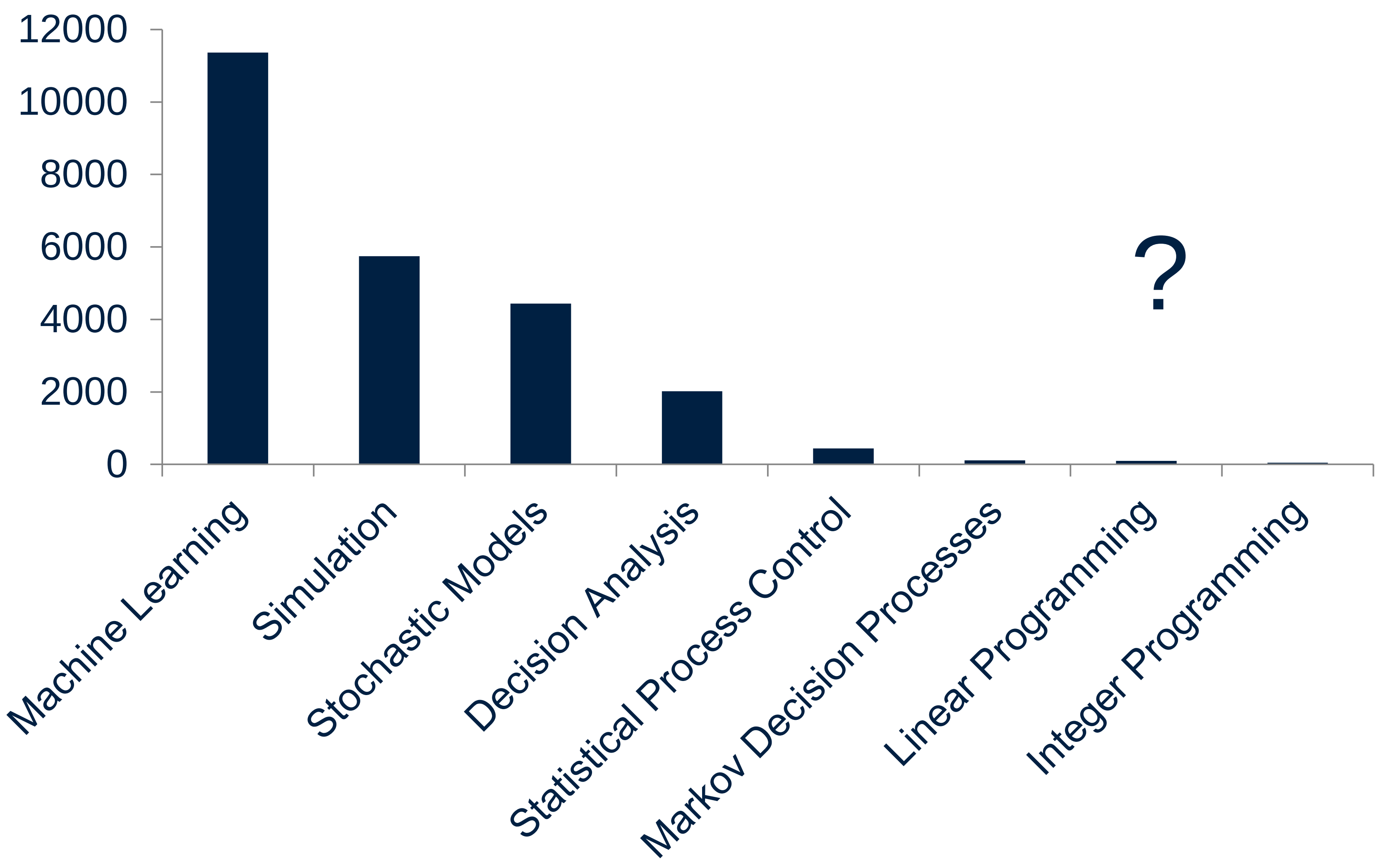
Kidney Disease

Heart Disease

Number of Publications on PubMed in the last 10 years

- 1,426,842 articles on cancer
  - 169,076 articles on breast cancer
  - 79,662 articles on prostate cancer
- 474, 417 articles on heart disease and stroke
- 304,406 articles on diabetes
- 43,887 articles on kidney disease
- 2,935 articles on allergies

PubMed Results Over the Last 10 Years



Claims

1. Optimization can improve medical decision making

2. Medicine can improve optimization

3. There are many unaddressed opportunities for future impact


PRESENT
FUTURE
PAST

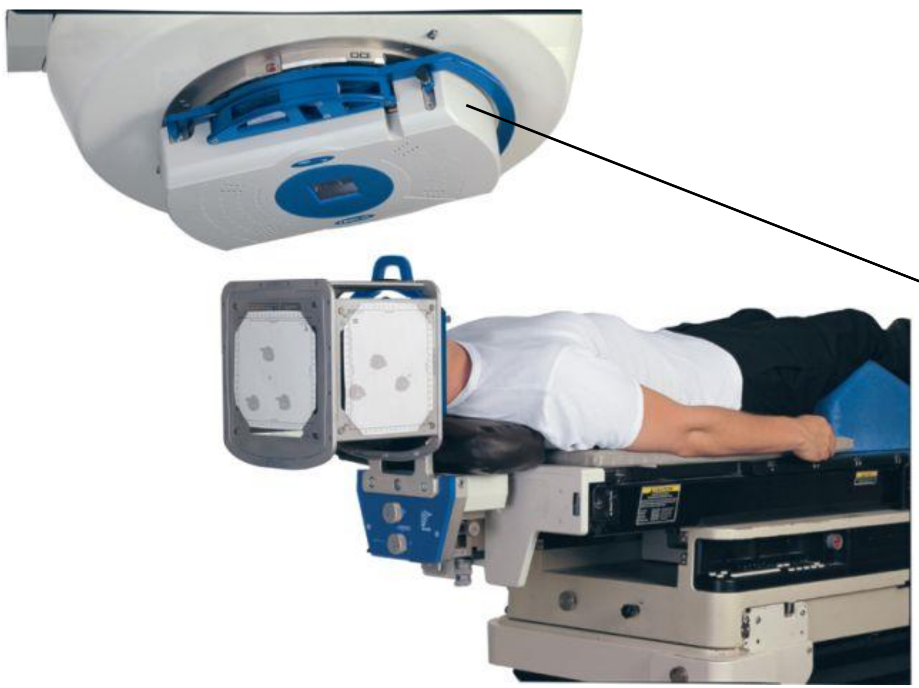
Example 1: Radiation Treatment

Bahr et al. 1968. “The Method of Linear Programming Applied to Radiation Treatment Planning.” *Radiology*. 91; 686-693.

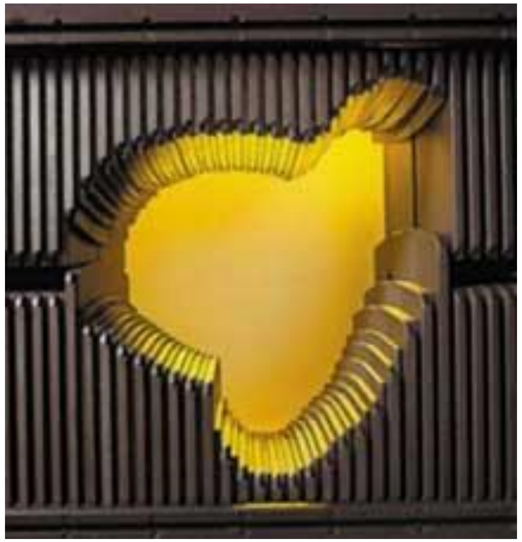
- External beam radiation is passed through the body harming cancerous and healthy tissue
- Objective: minimize damage to healthy tissue while delivering required dose to cancer tissue

Radiation is delivered via a rotating gantry with a multi-leaf collimator

Rotating Gantry

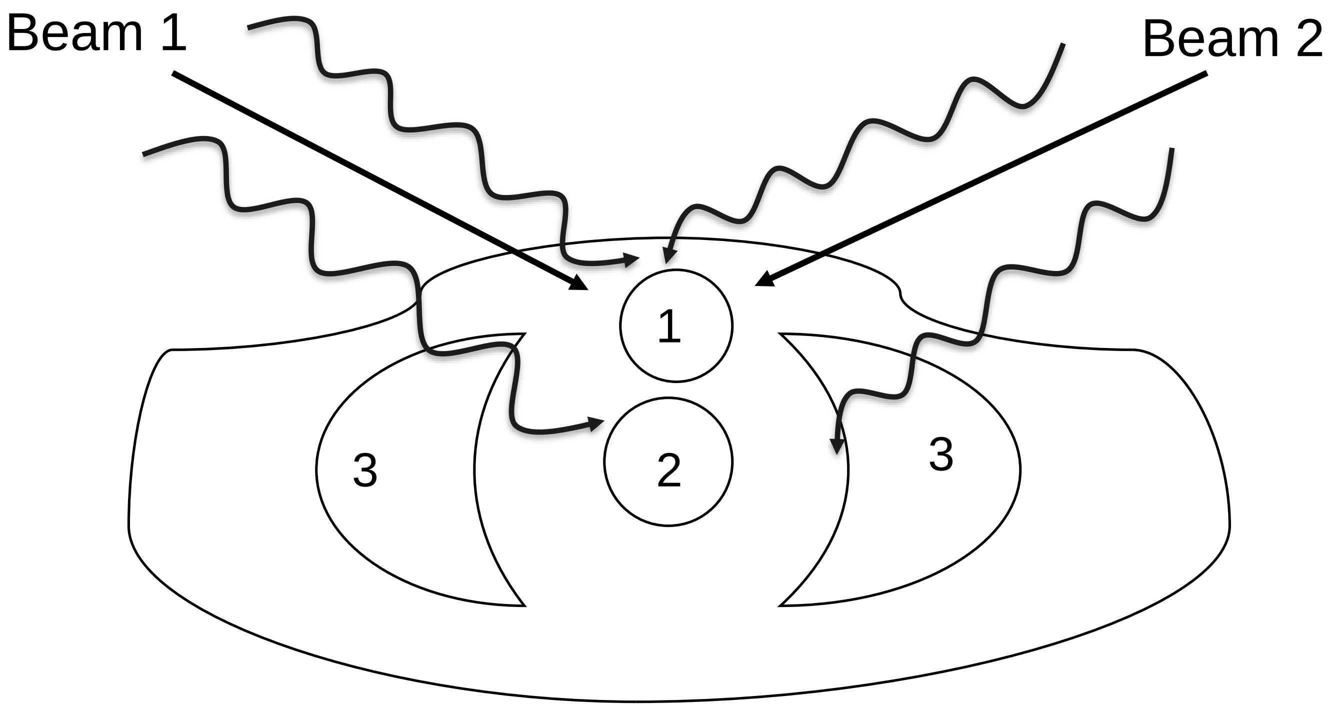


Multileaf Collimator



2-Beam Problem

1. Tumor
2. Spine
3. Brain

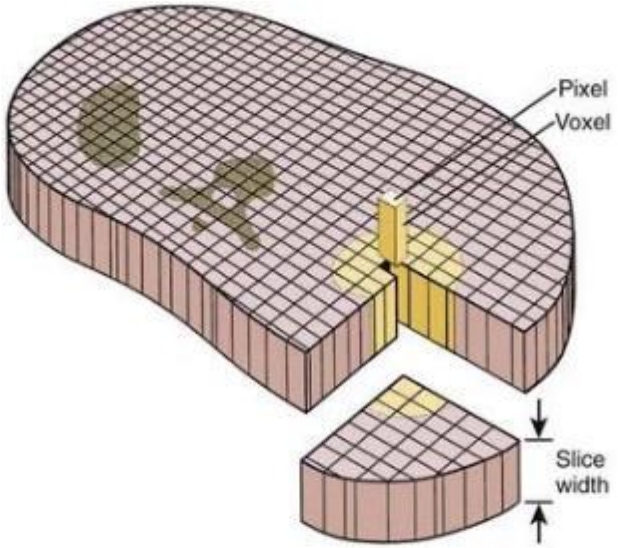


Linear Programming Model

Decision Variables: Exposure times for beams 1 and 2 (x_1, x_2)

Area	Dose Absorbed		Restriction on Dosage in Kilorads
	Beam 1 Dose	Beam 2 Dose	
Brain	0.4	0.5	Minimize
Spine	0.3	0.1	$\leq$ 2.7
Tumor	0.5	0.5	$=$ 6
Center of tumor	0.6	0.4	$\geq$ 6

Linear Programming Model



$$Min \ \ \sum_{\ell \in L} G_\ell(z)$$

$Subject\ to$:

$$z_j = \sum_{k \in K} D_{kj} x_k, \qquad for\ all\ j\ in\ V$$

$$x_k \geq 0, \ \ k \in K, \ \ z_j \geq 0, \ j \in V$$

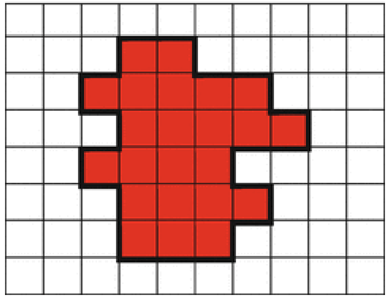
z_j: the dose delivered to voxel $j \in V$
x_k: the duration of beam $k \in K$

Extensions

Integrated optimization of aperture design and beam intensities:

- Predefined number of beams
- Each beam is decomposed into a rectangular grid with m rows and n columns to create an intensity matrix
  - For each row there are $\frac{1}{2}n(n-1)+1$ combinations of left and right leaf settings

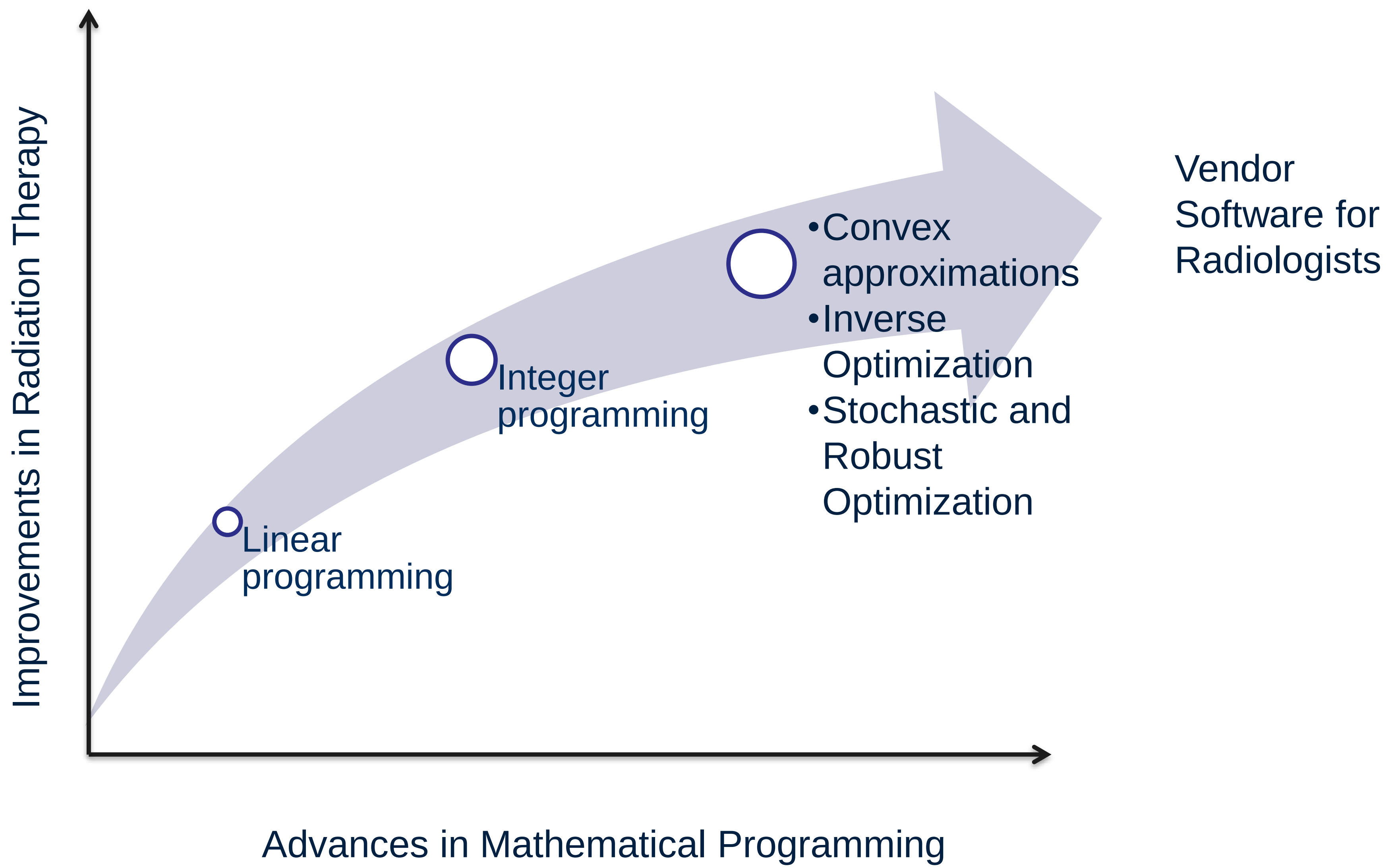
$$\Rightarrow \left(\frac{1}{2}n(n-1)+1\right)^m \quad \text{apertures}$$



- Column generation method: Start with a restricted set of apertures, price out new apertures (columns) via decomposition algorithms

Romeijn, E., Ahuja, R., Dempsey, J.F., Kumar, A. 2005. "A column generation approach to radiation therapy treatment planning using aperture modulation." *SIAM Journal on Optimization.* 15(3); 838-862.

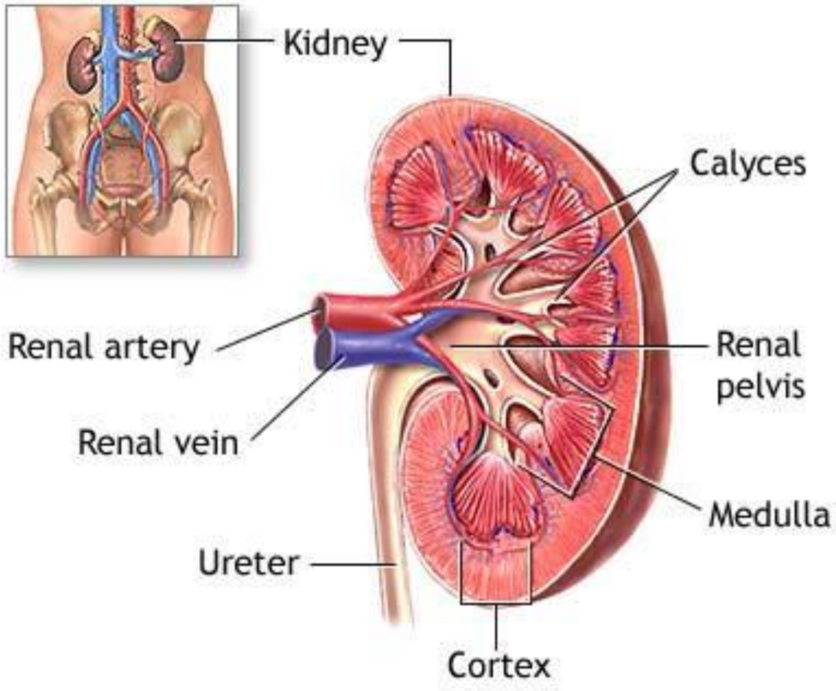
Path from Research to Implementation



Example 2: Kidney Disease

- Principal treatment options:
  - Dialysis (home or clinic)
  - Transplant (live or deceased donor)

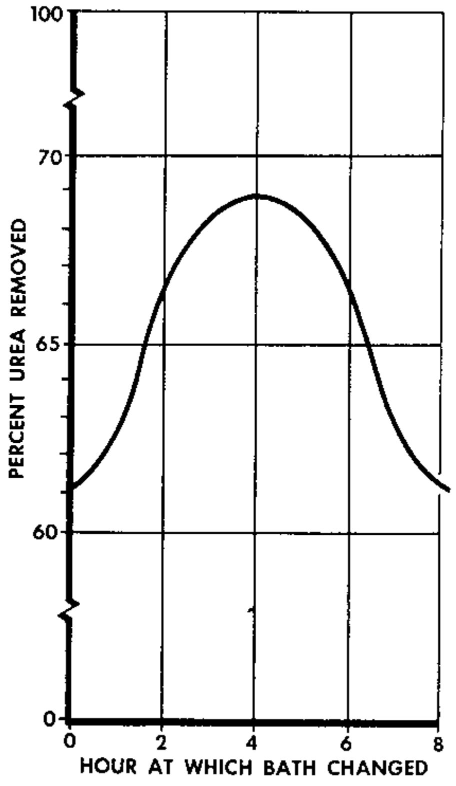
- More than 350,000 people are on dialysis and 80,000 waiting for transplant



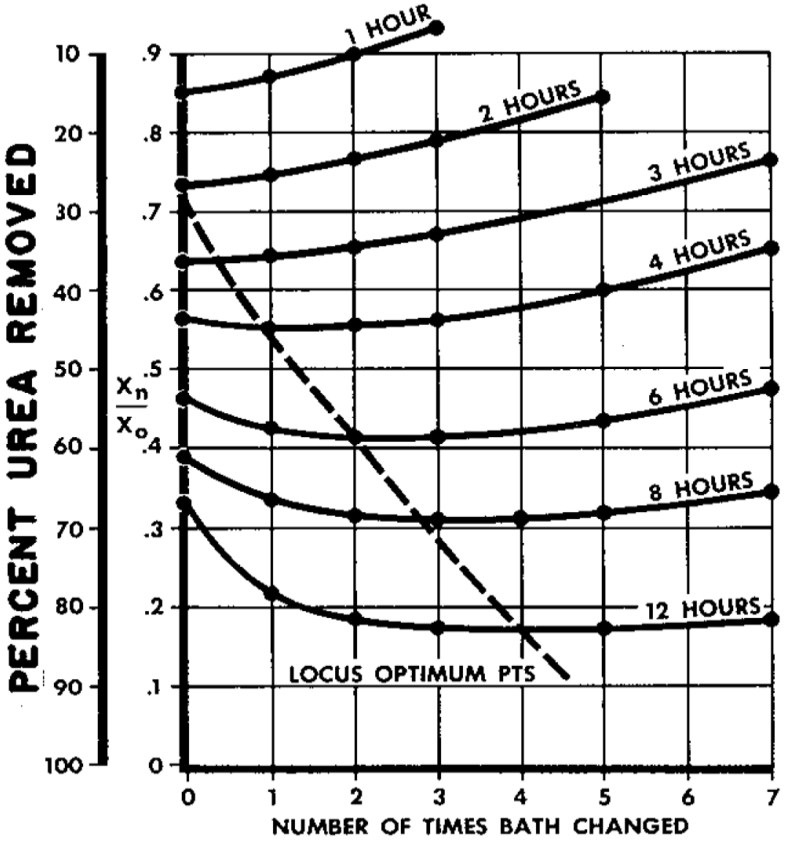
Nonlinear Optimization

Miller, J.H. et al. 1960. “Optimization of Certain Parameters in Hemodialysis,” *Transactions - American Society for Artificial Internal Organs*. 6(1); 68-75

Optimal time to change bath



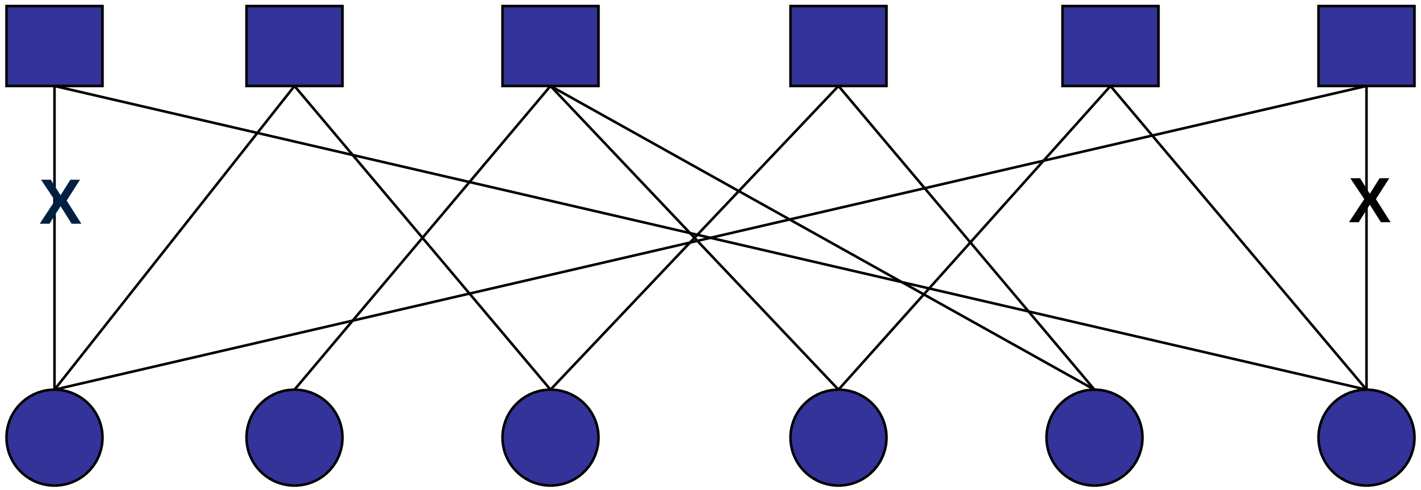
Optimal time to change bath



Optimization of Kidney Transplants

Kidney Exchange

Donors



Recipients

Paired Matching

Figure 1. Graph Theory Model of Donor/Recipient Nodes, With Links Indicating Compatible Matches

Segev, D, Gentry, S.E., Warren, D.S, Reeb, Montgomery, RA, 2005. “Kidney Paired Donation and Optimizing the Use of Live Donor Organs.” *JAMA.* 293(15), 1883-1890.

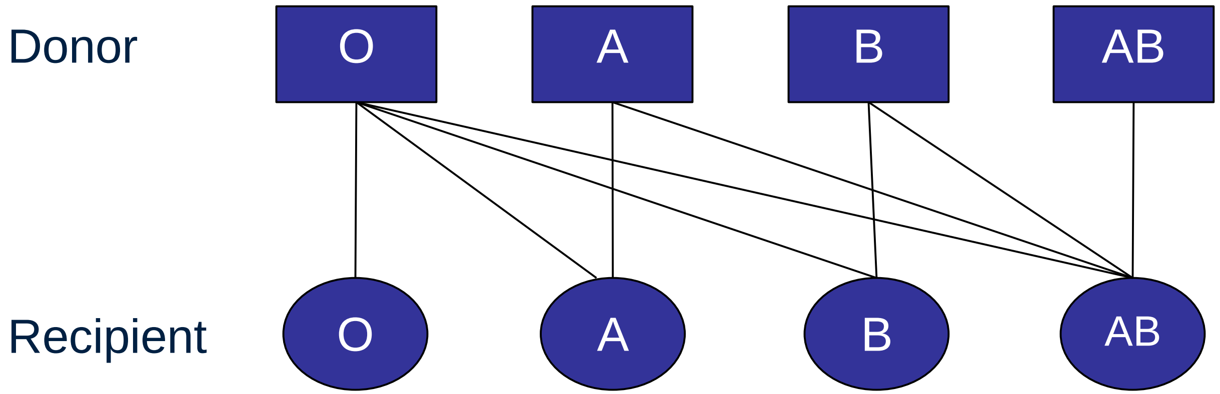
Criteria (Edge Weights)

- Number of matches
- Number of priority matches
- Immunologic concordance
- Travel requirements

Constraints (Edges)

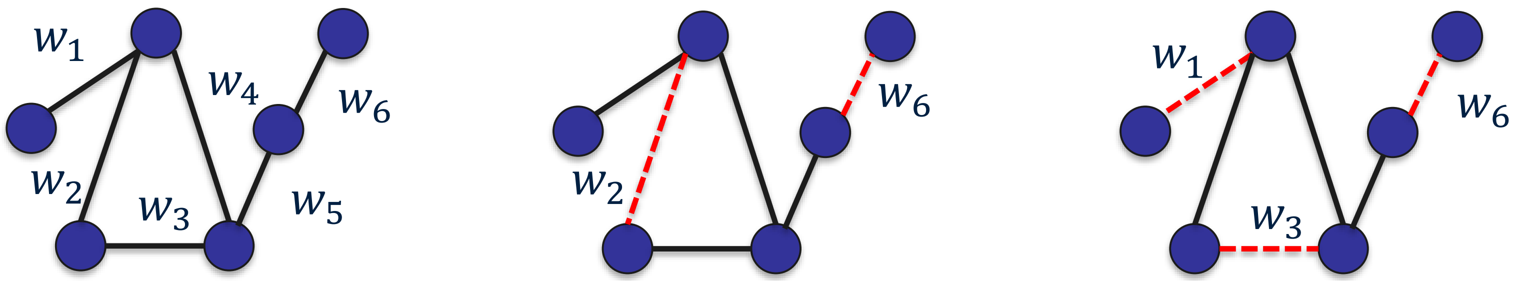
- Compatibility is determined by two primary factors:
  - Blood type
  - Tissue antibodies

- Blood type compatibility



Matching Problems

Given a graph $G(V,E)$ a *matching* is a set of pairwise nonadjacent edges.



2 matches

3 matches

A *maximal edge-weight matching* is a set of non-adjacent edges with maximum total weight among all matches.

Maximum Edge Weight Matching

A matching problem for a graph $G(V,E)$ can be expressed as an *integer program*

$$Max\ \ \sum_{e\in E} w_e x_e$$

$$Subject\ to:$$

$$\sum_{e\sim v} x_e \leq 1,\ \ for\ all\ v \in V$$

$$x_e \in \{0,1\},\ for\ all\ e \in E$$

Edmonds, J. 1965. "Paths, trees, and flowers," *Canadian J. Math*. 17; 449–467.

Factors that influence vertex and edge weights

- In a vertex weighted graph with positive weights any matching with maximum vertex weight has maximum cardinality

- A maximum edge weight matching could have **half as many** edges as a maximum cardinality matching

  - The ratio can be bounded by controlling : $\max_i w_i - \min_i w_i$

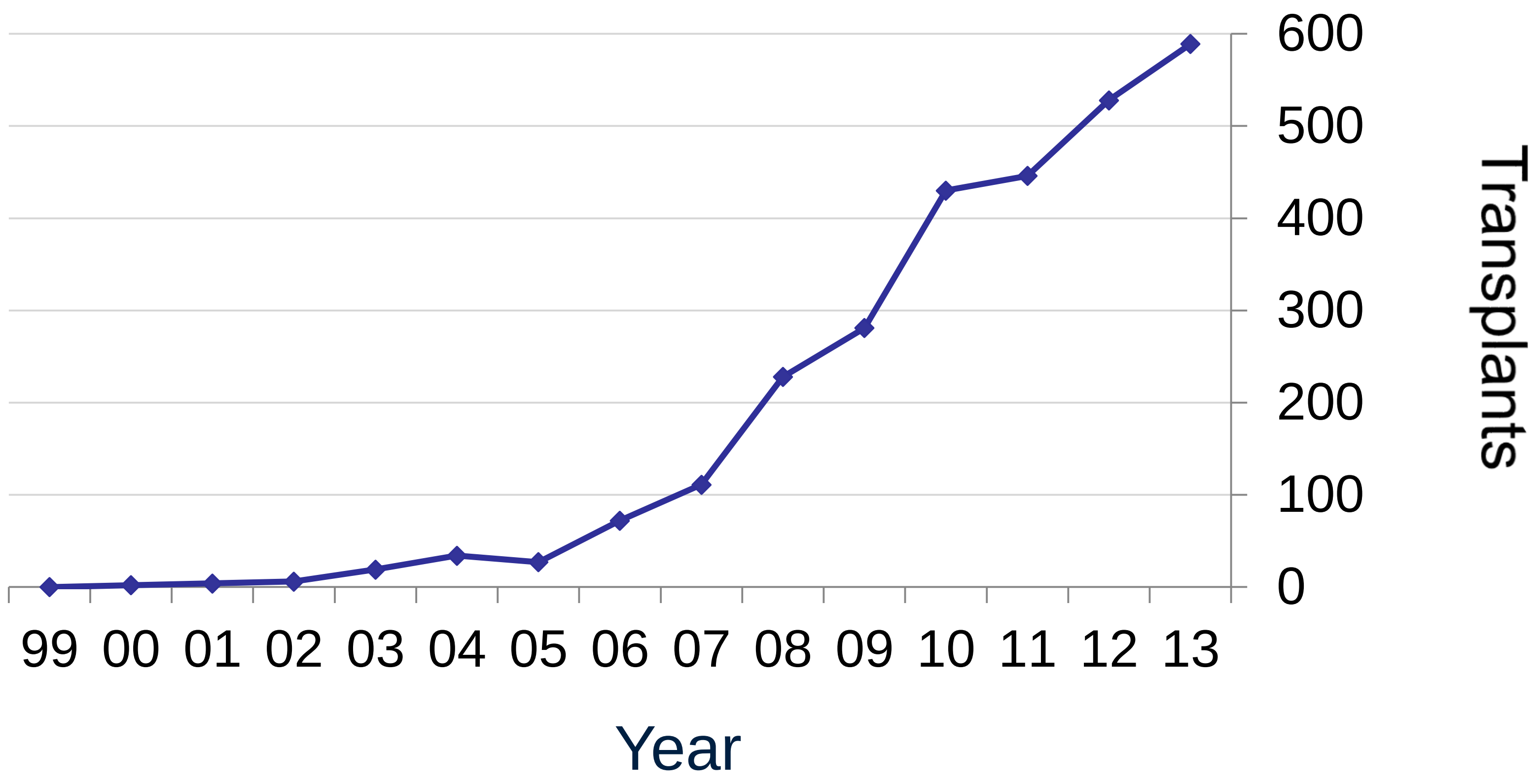
- Connections to multi-criteria problems:

    - Weighted objectives

    - Bi-level optimization

Gentry, S., Michael, T.S., Segev, D. “Maximum Matching in Graphs for Allocating Kidney Paired Donation,” Working Paper

Impact



From 1 in 1999, to nearly 600 in 2013, KPD now comprises 10% of living kidney donations**

*Figure courtesy of Sommer Gentry, US Naval Academy; www.optimizedmatch.com

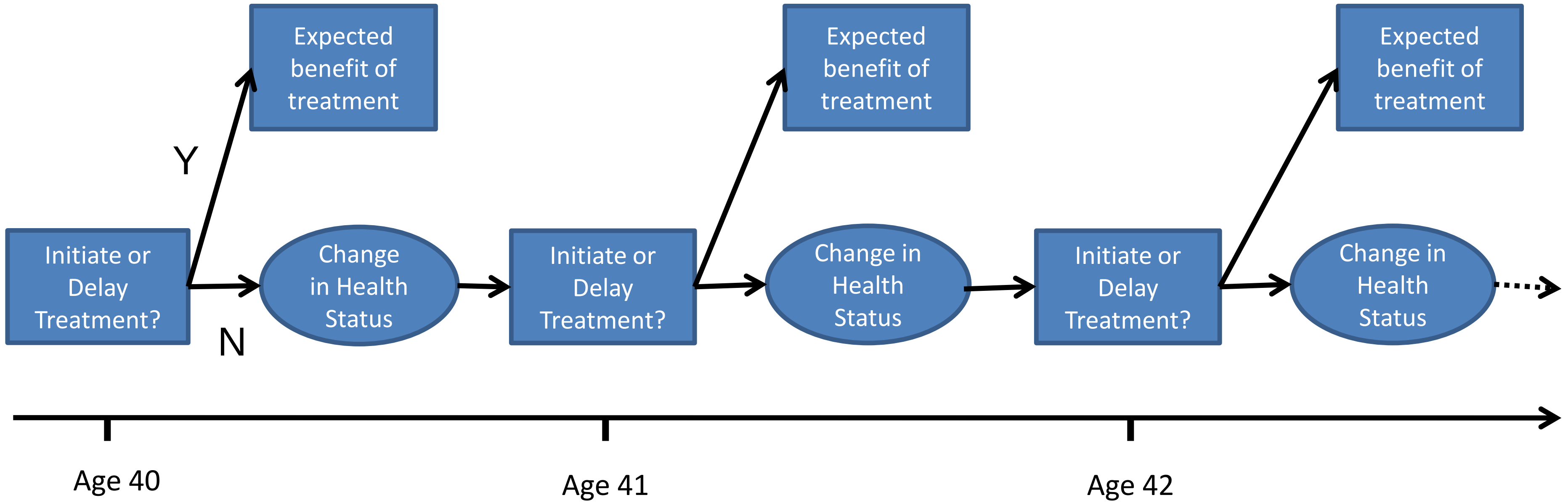
Example 3: Diabetes

- 29 million people have diabetes in the U.S.
  - 9% of the U.S. population
  - 90% have type 2 diabetes
- Health complications include micro and macro-vascular events
- Medication can control major risk factors like blood sugar, cholesterol and blood pressure

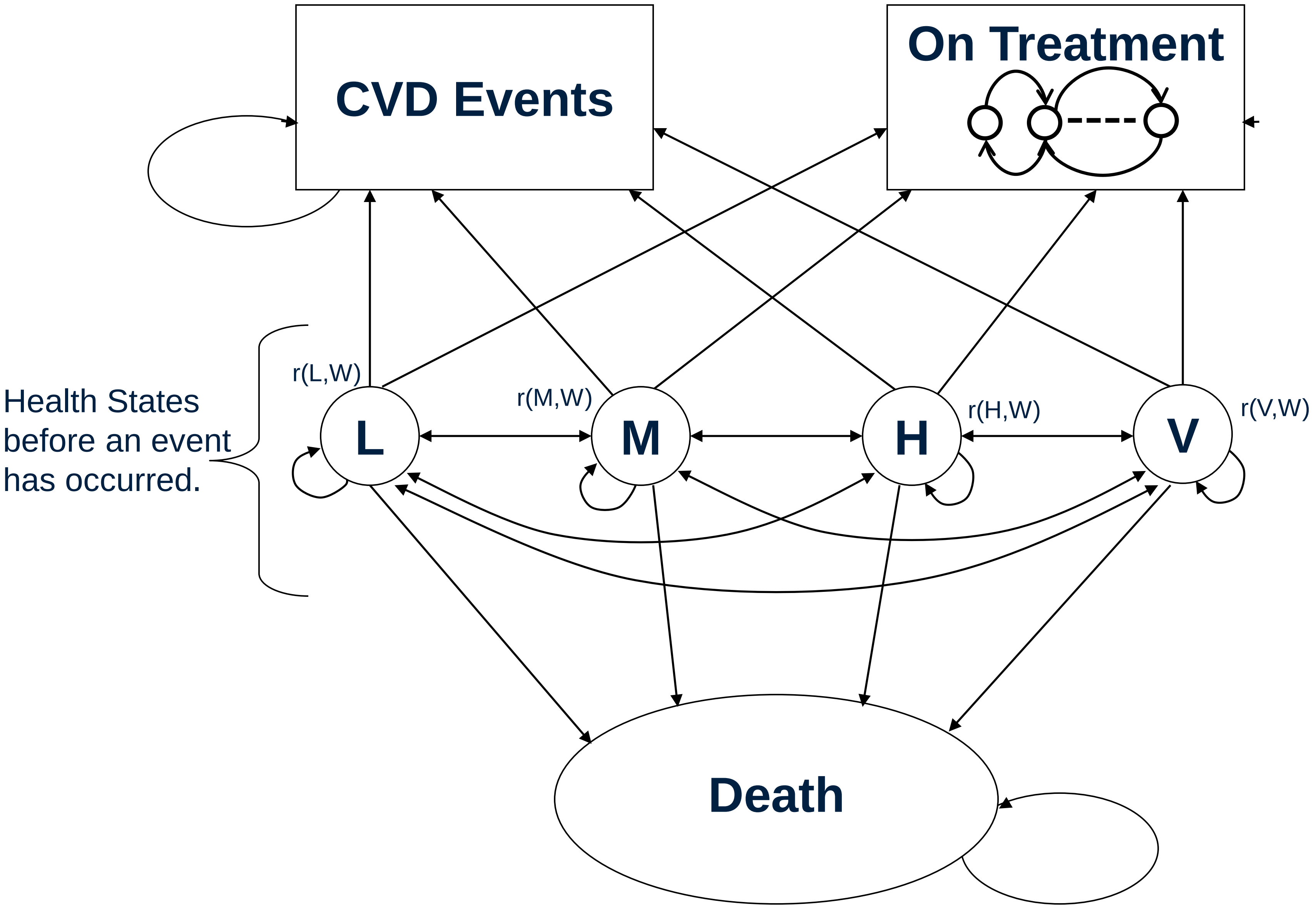
Mason, J.E. et al. 2014. “Optimizing the Simultaneous Management of Blood pressure and Cholesterol for Type 2 Diabetes Patients.” *European Journal of Operational Research.* 233(3); 727-738.

Sequential Decision Making

- Choose the best action each time period to maximize long term expected rewards



State Transition Diagram



Markov Decision Process

- Health status: $s_t \in S \equiv \{1,2,3,\ldots\ldots L, L+1\}$
- Treatment decision in state s_t: $a(s_t) \in A(s_t)$
- Optimality Equations for all $s_t, t = 1,\ldots,T-1$:

$$\overbrace{v_t(s_t)}^{\text{Optimal Reward to Go in Health State } s_t} = \max_{a_t}\{\overbrace{r(s_t,a_t)}^{\text{Period } t \text{ Reward}} + \overbrace{\lambda \sum_{\forall s_{t+1}} \underbrace{p(s_t'|s_t,a_t)}_{\text{Transition probabilities}} v_{t+1}(s_t')\}}^{\text{Discounted Expected Future Reward}}$$

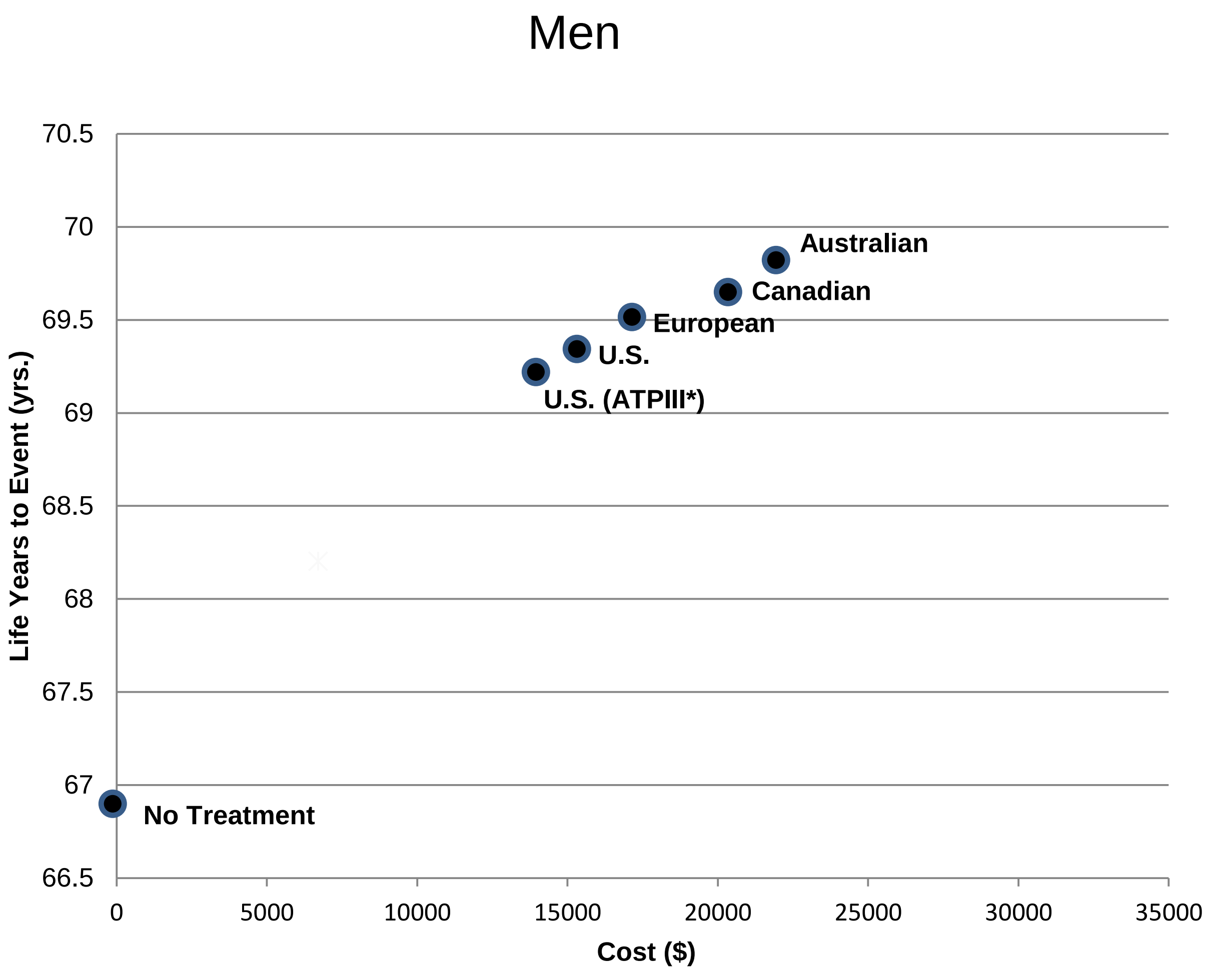
$$\underbrace{v_T(s_T) = r(s_T)}_{\text{Boundary condition}}$$

Reward Function

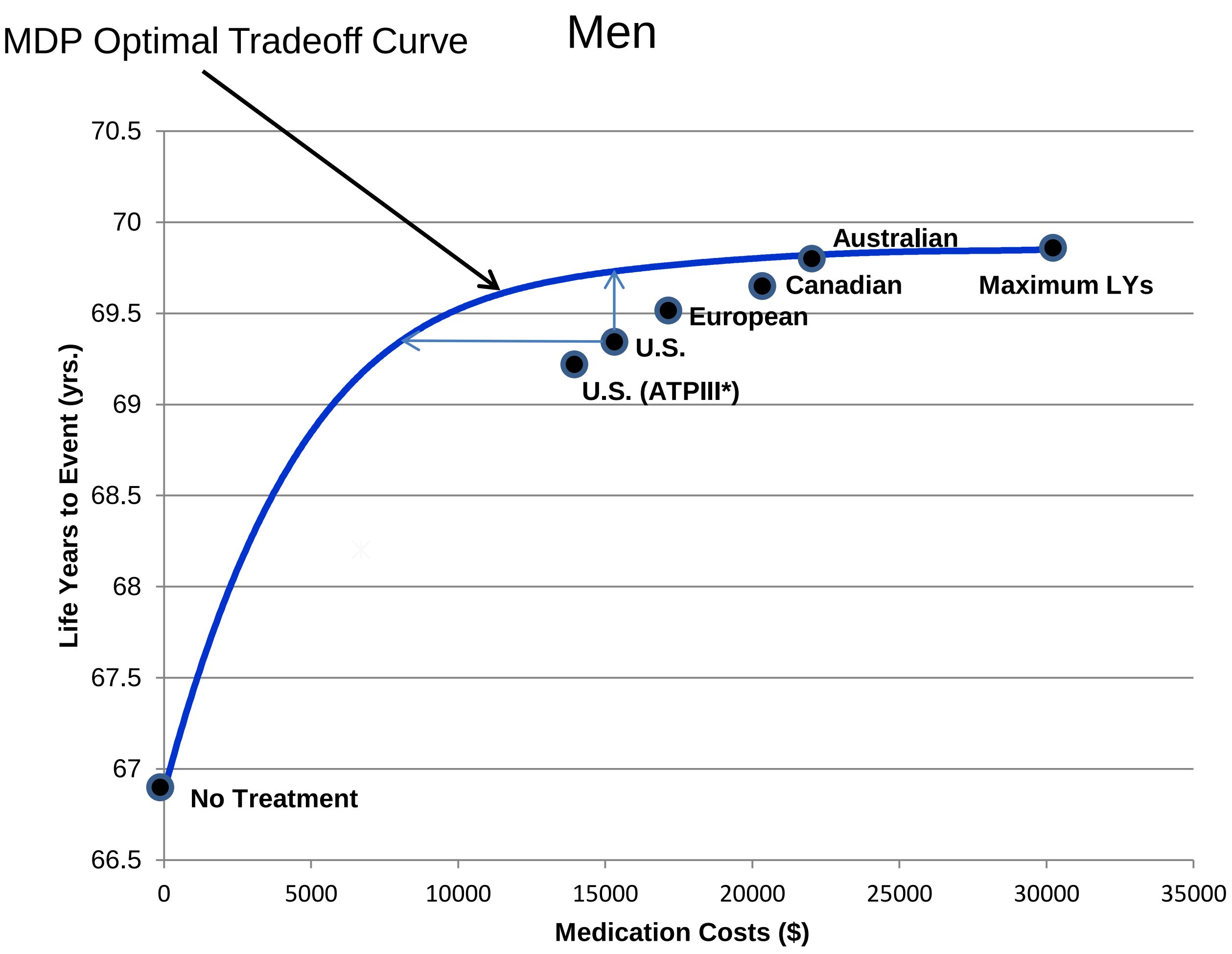
Rewards for each state action pair define the objective function for a Markov decision process

$$r(s_t, a_t) = \alpha \overbrace{L(s_t, a_t)}^{\text{Reward for living disease free for one period}} - (1-\alpha)(\overbrace{C^S(s_t) + C^{CHD}(s_t)}^{\text{Cost of cardiovascular events}} + \underbrace{C^M(s_t)}_{\text{Medication cost}})$$

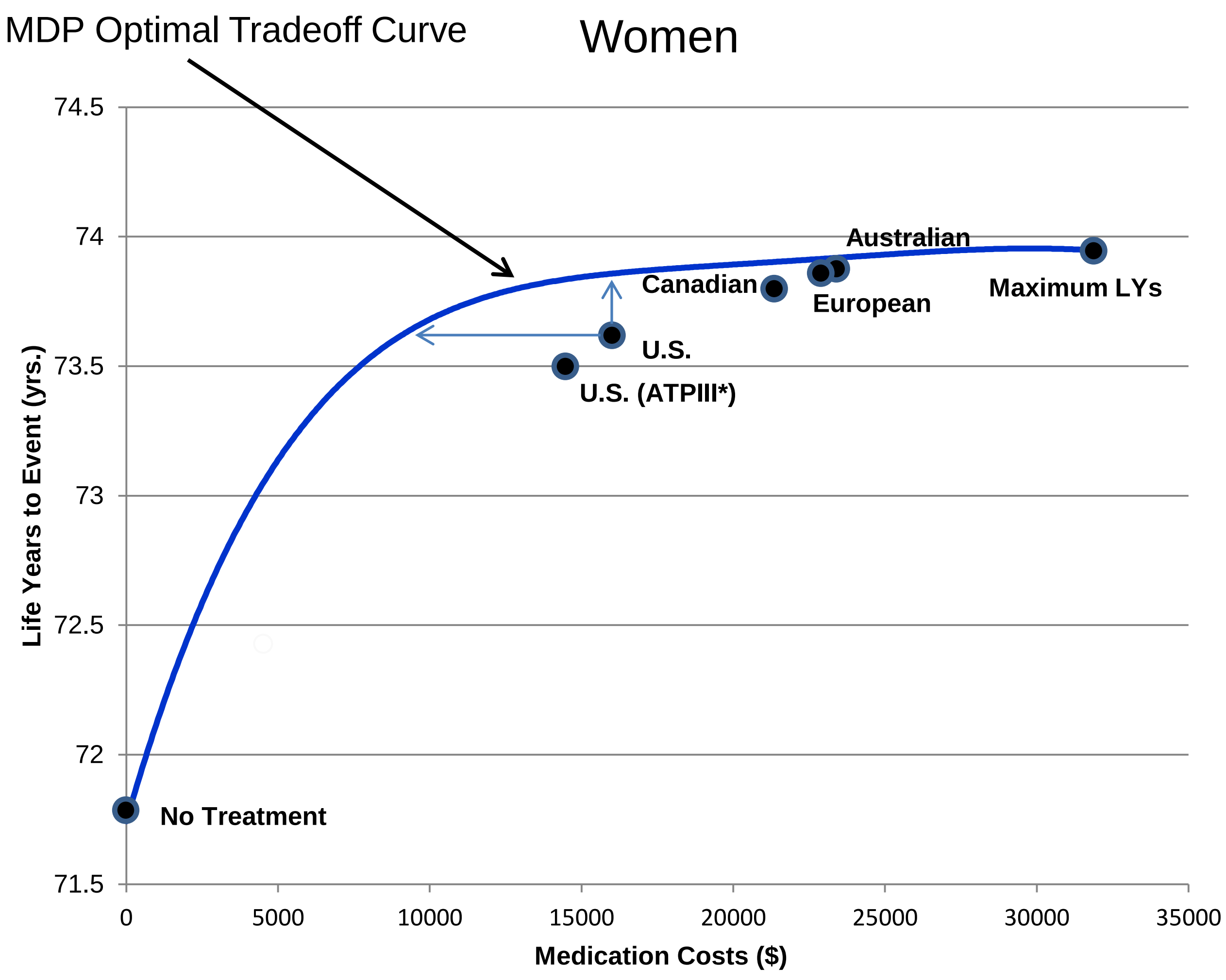
Policy Evaluation



Optimal Policy vs Guidelines



Optimal Policy vs Guidelines



Other Examples

- Liver Transplants: Alagoz, Maillart, Schaefer, Roberts, *Management Science*, 2004
- Breast Cancer: Maillart, Ivy, Ransom, Dielhl, *Operations Research*, 2008
- HIV: Shechter, Schaefer, Roberts, *Operations Research*, 2008
- Prostate Cancer: Zhang, Denton, Balasubramanian, Shah, *M&SOM* 2012
- Adherence to Screening: Ayer, Alagoz, Stout, Burnside, Management Science, 2015
- Colorectal Cancer: Erenay, Alagoz, Said, *M&SOM* , 2014

Markov Decision Processes for Screening and Treatment of Chronic Diseases

Markov Decision Processes in Practice pp 189-222

Part of the International Series in Operations Research & Management Science book series (ISOR, volume 248)

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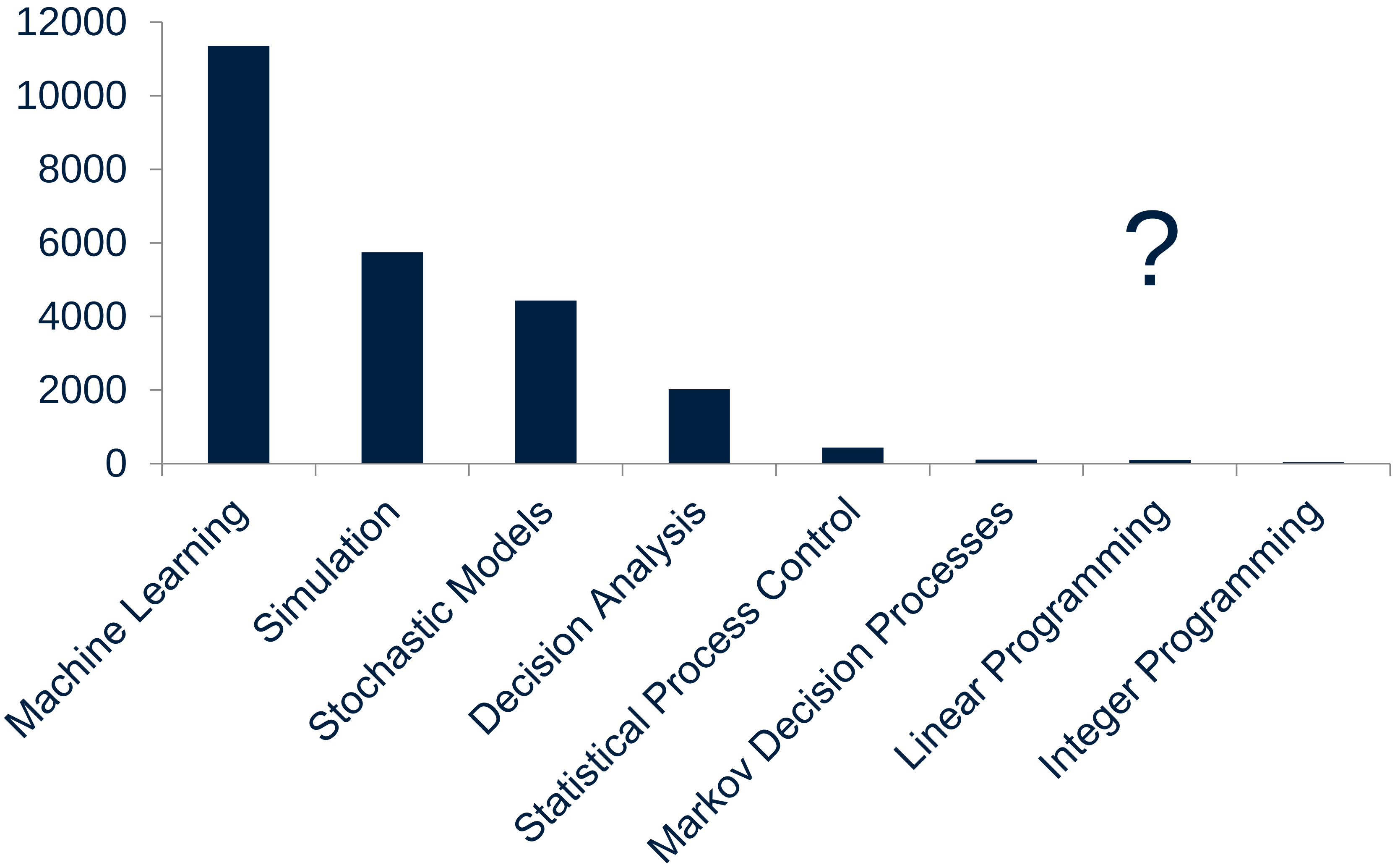
Optimization in Medicine:
The Future

PubMed Search Results



Sequential Decision Making

Research Questions:

- When and how frequently to screen for diseases?
- When to use diagnostic tests?
- When to treat?

Methods :

- Markov decision processes
- Partially observable Markov decision processes
- Multi-stage stochastic programming
- Reinforcement learning

Example

UVA's Continuous Closed-Loop Artificial Pancreas Powered by Android Smartphone

- Difficult real time optimal control problem
- Must maintain glucose levels within a defined range
- Current glucose state difficult to predict

Cobelli, C, Renard,E., Kovatchev, B. 2011. Artificial Pancreas: Past, Present, Future, *Diabetes*, 60, 2682 - 2682

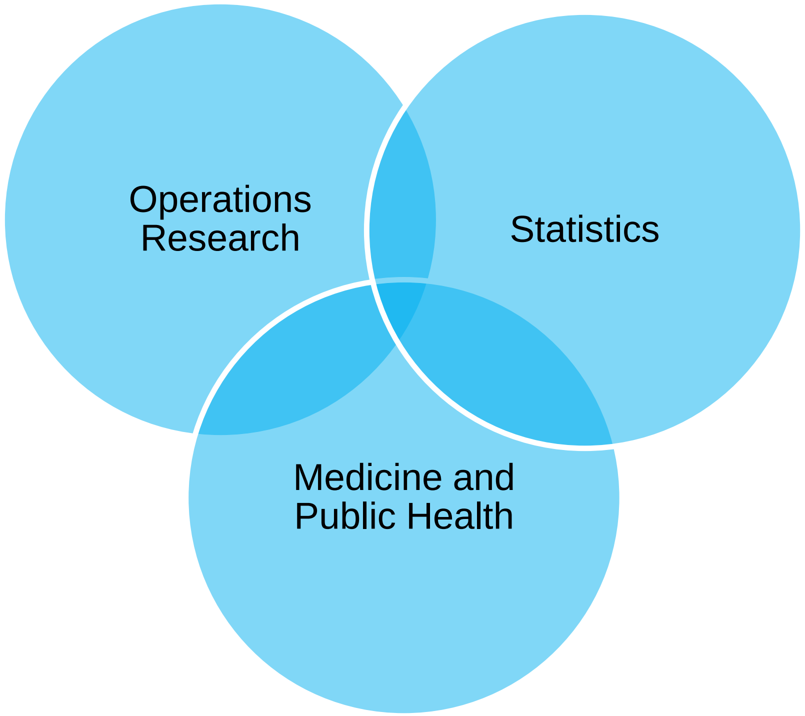
Resource Constrained Decision Making

Research Questions:

- How best to allocate resources across medical areas in hospitals?
- How to prioritize prevention and treatment in resource constrained settings?

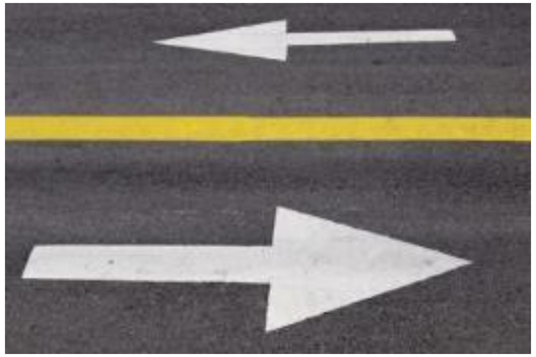
Methods:

- Continuous optimization
- Integer and combinatorial optimization
- Stochastic Programming



Takeaways

- <u>Optimization</u> models can improve medical decision making and vice versa but…



- It is underutilized and there are many challenges and unexplored <u>opportunities</u> to address this problem

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